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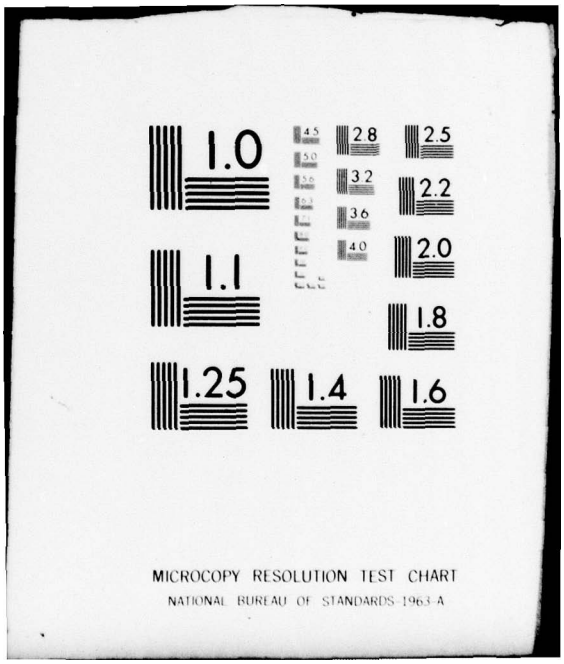
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EVALUATION OF THE HEALTH ASPECTS OF CERTAIN COMPOUNDS FOUND IN IRRADIATED BEEF

SUPPLEMENT I. - A045716
FURTHER TOXICOLOGICAL CONSIDERATIONS
OF VOLATILE COMPOUNDS

March 1979

Prepared for

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
DEPARTMENT OF THE ARMY
FORT DETRICK, FREDERICK, MD 21701

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The recent literature is reviewed of the volatile compounds identified in irradiated beef. Of particular interest were the regulatory actions initiated by the Occupational Safety and Health Administration reducing the maximum acceptable concentration of benzene in the workplace atmosphere from 10 to 1 parts per million, because of the suspected leukemogenic action of the compound. This action is being contested in the courts. Hexane and toluene have been shown to produce neurologic symptoms when inhaled in high

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concentrations to achieve a state of euphoria. Some evidence suggests that methyl ethyl ketone (2-butanone) may have similar effects in inhalant abusers. Each of these compounds is found in irradiated beef but at levels several orders of magnitude less than those producing these toxic effects. The authors conclude that there is no evidence that consumption of reasonable quantities of beef irradiated in the described manner would constitute a hazard to health.

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EVALUATION OF THE HEALTH ASPECTS OF CERTAIN COMPOUNDS FOUND IN IRRADIATED BEEF

SUPPLEMENT I

FURTHER TOXICOLOGICAL CONSIDERATIONS OF VOLATILE COMPOUNDS

March, 1979

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SUMMARY

The U.S. Army has developed a process for the preservation of beef by high-dose irradiation in vacuo at about -30°C. A total of 65 volatile compounds in concentrations of 1 to 700 μg per kg was identified in the irradiated beef. A number of these were also found in equal or greater concentrations in nonirradiated beef samples. Most of the radiolytic products were saturated and unsaturated aliphatic hydrocarbons, containing 2 to 17 carbon atoms. There were, in addition, several alcohol, aldehyde, and ketone derivatives, the aromatic hydrocarbons benzene and toluene, and two sulfur-containing compounds. In 1977, the Select Committee on Health Aspects of Irradiated Beef reviewed critically the available data on each of these compounds and concluded that the evidence indicated no grounds to suspect them of constituting a hazard to health to persons consuming reasonable quantities of beef irradiated in the described manner.

Since this 1977 report by the Select Committee, additional publications have appeared on the biological effects of some of these compounds. In addition several government agencies are scrutinizing the possible toxic effects of benzene and toluene because of their ready availability to the public and the exposure of industrial workers to their vapors. For these reasons, it was deemed desirable to review once again any possible hazard of known radiolytic products from beef in the light of newly available data.

Upon careful review of recent studies, the Select Committee found little relevant, supplementary information on the compounds under consideration. Several reports attest to the neurotoxicity of hexane and toluene when these solvents are inhaled repeatedly and intentionally to induce euphoria. More stringent standards have been imposed for permissible levels of benzene in the workplace, but these are now being contested in the courts. New data suggest that methyl ethyl ketone may accentuate neuropathies induced by hexane or methyl n-butyl ketone. The exposure levels of these substances in the environment or upon voluntary inhalation are far higher than are possible from irradiated beef or from various natural food sources in which these compounds are also found. Few recent reports were concerned with the other volatile compounds found in irradiated beef.

Since the reported toxicities of the above compounds occur only at exposures several orders of magnitude greater than found in irradiated beef, the Select Committee reaffirms its original conclusion that the volatile radiolytic compounds appear to pose little or no health hazard when reasonable quantities of beef irradiated in the described manner are consumed.

FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and opinions of knowledgeable investigators who are actively working in specific areas of biology and medicine.

A technical report entitled "Evaluation of the Health Aspects of Certain Compounds Found in Irradiated Beef" (AD-A045716) was published in August, 1977 by an *ad hoc* Select Committee with the assistance of the LSRO staff. It reviewed the biological effects of 65 volatile compounds found in irradiated beef. The present report supplements this earlier review with material which has subsequently come to the attention of the Committee.

The Select Committee accepts the responsibility for the contents of this report. Special appreciation is expressed to Dr. Walter M. Urbain, Special Consultant, for his helpful comments in the preparation of this report. The report was approved by the Select Committee, the Director of LSRO, and by the LSRO Advisory Committee composed of representatives of each constituent society of FASEB, under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to the U.S. Army Medical Research and Development Command by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

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I. INTRODUCTION

As part of a continuing study on the wholesomeness of irradiated meats, the Food Sciences Laboratory of the U.S. Natick Research and Development Command has determined the volatile compounds produced when beef is treated at about -30°C with 56 kGy (5.6 Mrads) of gamma ray or high energy electron radiation. Sixty-five compounds were identified after irradiation with concentrations ranging from 1 to 700 μg per kg beef (parts per billion). Some of these compounds were of radiolytic origin while others were present in equal or greater amounts in nonirradiated samples. The health aspects of each of these compounds, whether radiolytic or nonradiolytic, were reviewed by a Select Committee assembled by the Life Sciences Research Office (1977). This report is intended to supplement the earlier review by consideration of recent publications and additional information which have subsequently come to the attention of the Committee. A complete listing of all compounds and their concentrations is given in the original report.

II. COMPOUNDS DETECTED*

A. HYDROCARBONS

1. Alkanes (pp. 37-46)
2. Alkenes and alkynes (pp. 47-55)

The entire series of normal alkanes and alkenes from C-2 to C-17 were found in irradiated beef. The concentrations ranged from 164 to 696 μg per kg for alkanes and from 28 to 618 μg per kg for alkenes. Small amounts (19 to 45 μg per kg) of the 2-methyl isomers of propane, propene, butane, pentane, and heptane were also present. In addition, two alkynes (decyne and undecyne: 23 and 4 μg per kg) and four dienes (tetra-, penta-, hexa-, and heptadecadiene: 16 to 706 μg per kg) were identified.

Of these aliphatic hydrocarbons, hexane (209 μg per kg irradiated beef) has been the most thoroughly investigated. It is used as a solvent in glues, varnishes, cements, inks, and a number of other products (National Institute for Occupational Safety and Health, 1977). Significant and repeated exposures to this compound are largely confined to two groups of individuals: the industrial worker and the abuser of inhalants. The former group is exposed because of workroom contamination while individuals in the latter group deliberately expose themselves to achieve a state of euphoria or "high".

The acute toxicities of the volatile alkanes are relatively low; allowable concentrations in workplace atmospheres range from 100 parts per million (ppm; 360 mg per m^3) for hexane to several thousand ppm (>2000 mg per m^3) for the simplest homologues: methane, ethane, propane (American Conference of Governmental Industrial Hygienists, 1976). However, numerous reports attest to the toxicity for man (Oishi et al., 1964; Yamamura, 1969; Herskowitz et al., 1971) and animals (Miyagaki, 1967; Ishii et al., 1972 Schaumburg and Spencer, 1976) of chronic exposure to hexane or hexane-containing solvents. Yamamura (1969) conducted a comprehensive clinical study and reported nerve damage in 93 of 1662 workers who were exposed to hexane in an industrial setting. He estimated that the affected individuals had been exposed to concentrations of 500 to 2500 ppm (1.8 to 9.0 g per m^3 of hexane for 8 hours or more daily, 6 or 7 days weekly for several months or more. Similarly, Yamada (1967) described 17 cases of polyneuropathy among workers in small laminating plants with atmospheric hexane concentrations of 1000 to 2500 ppm and in pharmaceutical plants with 500 to 1000 ppm. Symptoms of intoxication appeared within 1 to 2 months after initial exposure. Herskowitz et al. (1971) reported three cases of polyneuropathy among factory

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*Page citations refer to the original report (LSRO, 1977) which should be consulted for additional details.

workers exposed to an average of 650 ppm hexane for 2 to 4 months. The observed human neuropathies involved both the sensory and motor systems, with characteristic manifestations of muscular weakness or atrophy, hypesthesia, and hypoactive reflexes.

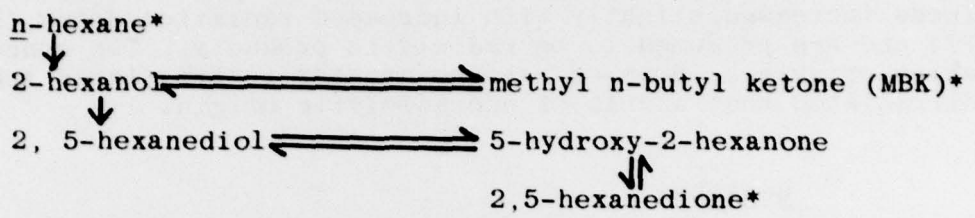
More recent studies including both industrial exposure (Paulson and Waylonis, 1976) and solvent abuse (Gonzalez and Downey, 1972 Goto et al., 1974, Towfighi et al., 1976) have confirmed these earlier findings. Although other volatile compounds were present in the inhaled solvents, hexane appeared to be the major contributor to the observed toxicity. Some of the inhalant-abuse patients had inhaled hexane-free volatiles for years without apparent detrimental effect, but had developed crippling peripheral neuropathy within a matter of months after switching to products containing hexane (Bruckner and Peterson, 1977).

Experimental demonstration of the neurotoxicity of hexane was provided by Schaumburg and Spencer (1976) who observed degenerative neurological changes in adult Sprague-Dawley rats inhaling highly purified hexane (400 to 600 ppm) continuously for 162 days or receiving 550 to 2000 mg per kg of the compound subcutaneously 5 days weekly for 18 to 35 weeks. Degeneration in the central and peripheral nervous systems was noted in both groups of animals within 2 to 3 months. Widespread axonal degeneration in the central nervous system was regularly observed and was similar to that reported in nerve biopsies from patients inhaling glue vapors containing hexane (Goto et al., 1974; Korobkin et al., 1975).

The most apparent effects of hexane poisoning are upon the nervous system; evidence of damage to other tissues is scanty. Paulson and Waylonis (1976) observed elevated serum levels of lactic dehydrogenase and glutamic oxaloacetic transaminase which suggested liver damage in one patient with hexane-induced neuropathy. Nix et al. (1977) reported liver damage in mice exposed to high atmospheric concentrations (6000 to 12000 ppm) of mixed hexanes for 2 to 49 days. Hepatic lipid accumulation was noted in rats (Bohlen et al., 1973) and in guinea pigs (DiVincenzo and Krasavage, 1974) after hexane inhalation. No reports have been found of toxicity induced by hexane concentrations below the maximum allowable concentration in workroom atmospheres (100 ppm).

It now appears that a metabolic product, 2,5-hexanedione rather than hexane itself, is the active neurotoxic agent. Cats given 0.5 percent of this product in drinking water for periods up to 136 days developed widespread axonal degeneration similar to that observed with hexane intoxication (Schaumburg and Spencer, 1978). Methyl n-butyl ketone, also believed to be a hexane metabolite, has produced similar neurologic damage in industrial workers (Allen et al., 1974) and experimental animals (Duckett et al., 1974, DiVincenzo et al., 1978).

The interrelationship of these compounds is suggested in the following scheme (DiVincenzo et al., 1976, Nix et al., 1977):



*demonstrated neurotoxic agents

Hexane and related compounds appear to be metabolized by an inducible microsomal enzyme system. When mice were continuously exposed to an atmosphere containing 2.5 to 3 percent hexane, the monooxygenase capacity of the liver increased dramatically (Krämer et al., 1974). Three isomeric alcohols were formed from hexane by the liver microsomes, with 2-hexanol predominating. Couri et al. (1978) also found 2-hexanol in the urine of guinea pigs after intraperitoneal injection of n-hexane. When the guinea pigs were pretreated with phenobarbital, the urinary 2-hexanol increased.

Staples and Marks (1979) are currently studying the possible teratogenic effects of n-hexane in pregnant CD1 Charles River mice. No results are yet available.

The Committee knows of no study demonstrating a neurotoxic effect of the other alkanes identified in irradiated beef. However, Gaultier et al. (1973) reported polyneuropathy in five workers exposed to a solvent containing 80 percent pentane, 14 percent heptane, and 5 percent hexane. They suggested that pentane or heptane, rather than hexane, might be responsible for the observed neurologic damage. Indirect support for this suggestion comes from the observations of Frommer et al. (1972) who noted that rat liver microsomal preparations hydroxylate other low and medium-length alkanes as well as hexane. Thus, all possible isomeric heptanols were produced when heptane was incubated with microsomal preparations, with 2-heptanol predominating. This reaction is analogous to that found with hexane (Krämer et al., 1974), in which microsomal incubation also hydroxylated all possible positions, with a preponderance of 2-hexanol.

No additional pertinent information has been found for the other aliphatic hydrocarbons of irradiated beef.

3. Aromatic Hydrocarbons (pp. 56-67)

Benzene, toluene, and xylene were detected in small amounts (<0.1 ppm) in the irradiated beef samples. Benzene and toluene increased slightly with increased radiation doses (LSRO, 1977) and are presumed to be radiolytic products. The concentration of xylene, however, was no greater in irradiated than in nonirradiated beef and is of nonradiolytic origin.

Benzene

A voluminous literature exists on the toxicity and metabolism of benzene. The major area of interest has been the effect in man of chronic inhalation of its vapor; this aspect has been reviewed comprehensively in several recent reports (NIOSH, 1974, National Research Council, 1976, Haley 1977, Occupational Safety and Health Administration, 1978). A leukemogenic action has long been suspected because of the occurrence of leukemia among some workers chronically exposed to benzene (NRC, 1976; Aksoy, 1978). Although the affected individuals had also been exposed in most cases to other compounds in the work place, benzene appeared to be the common agent. Early epidemiologic surveys yielded conflicting results. In one major study, an annual incidence of 13 cases of leukemia per 100,000 persons was found among 28,500 shoeworkers exposed to benzene, compared with 6 cases per 100,000 among the general population (Aksoy et al., 1974). However, there was no greater incidence of leukemia among 38,000 petroleum workers potentially exposed to benzene than among unexposed individuals (Thorpe, 1974). Reviewing the available data, the NIOSH (1974) concluded that "the possibility that benzene can induce leukemia cannot be dismissed," but it emphasized the need for additional, careful, epidemiologic studies.

Since this NIOSH review, additional reports have appeared suggesting a relationship between benzene exposure and leukemia (McMichael et al., 1975, 1976, Andjelkovic et al., 1976, Monson and Nakano, 1976, Infante et al., 1977a; Ott et al., 1978). Of especial interest was the survey of workers involved in the production of Pliofilm® (Infante et al. 1977a,b). In this survey the influence of other solvents was largely excluded, for in addition to benzene, the workers were exposed only to hydrochloric acid, soda ash, and small amounts of antioxidants and plasticizers. Workers occupationally exposed to benzene during the years 1940 to 1949 were followed for vital status up to 1975. Of 748 workers exposed during this period, seven died from myelogenous or monocytic leukemia, an incidence seven times that observed in the general population or in workers not exposed to benzene ($P<0.002$). The level of exposure to benzene by the workers during this period (1940-1949) is uncertain. In 1941, the maximum allowable concentration was 100 ppm which was lowered to 50 ppm in 1947 and to 35

ppm in 1948 for an 8-hour time-weighted average (Infante et al., 1977b). Since 1971, the allowable concentration has been 10 ppm. The statistical treatment in this study by Infante et al. (1977a,b) was criticized by Tabershaw and Lamm (1977), but defended by the original investigators (Infante et al., 1977c).

The NIOSH report (1976) concluded that the clinical and epidemiologic evidence demonstrated the leukemogenicity of benzene in man. The report recommended that no worker be exposed to air concentrations in excess of 1 ppm (3.2 mg per m^3) on a time-weighted average. This recommendation was adopted by OSHA (1977), which established emergency temporary standards on May 3, 1977, reducing the permitted employee exposure to benzene from 10 ppm to 1 ppm based on an 8-hour time-weighted average. On February 10, 1978, these levels were adopted as the permanent standard for the regulation of worker exposure to benzene (OSHA, 1978). Industry contested these regulations, arguing that experimental evidence was lacking that benzene at the existing authorized level of 10 ppm was harmful. In October 1978, the Fifth Circuit Court of Appeals in New Orleans ruled against OSHA. The Supreme Court has agreed to review the ruling and a final decision is expected in 1980 (Carter, 1979).

In June, 1977, the Environmental Protection Agency (EPA, 1977) also concluded that the evidence implicating benzene as a leukemogenic agent was sufficiently strong to merit its addition to the list of hazardous air pollutants.

The opinion that benzene is leukemogenic is not accepted by all investigators. Their reluctance to label benzene a carcinogen has rested both upon the poor quality of human epidemiologic data and upon a consistent failure to produce leukemia or cancerous tumors in experimental animals (NRC, 1976; Ward et al., 1975). Pancytopenia has been produced in animals by benzene injection (Kissling and Speck, 1972), but experimentally induced leukemias or carcinomas have not been reported. At a recent seminar, Maltoni claimed that he had produced various tumors in rats by feeding benzene for periods up to 76 weeks (Anonymous, 1977). Of 70 rats fed 250 mg benzene per kg body weight, five developed tumors of the Zymbal gland, five had dermal tumors, and three a "variety of other rare tumors". No leukemias were reported. Of 60 rats fed 50 mg per kg, two had Zymbal gland tumors and one a dermal tumor. None of more than 300 control rats developed tumors of any type. A detailed account of this study has not yet appeared in a scientific journal.

Despite numerous metabolic studies, both in vitro and in vivo, the mechanism of benzene action on the hematopoietic system remains unclear. Some workers have attributed the toxicity to benzene itself (Ikeda et al., 1972), while others believe a metabolite is responsible (Lee et al., 1974). In an attempt to resolve this controversy, Timbrell and Mitchell (1977) studied the

effects of various microsomal enzyme inducers and inhibitors. If benzene itself were the toxic agent, metabolic inhibitors would be expected to increase, and metabolic inducers to decrease, the toxicity of benzene. The opposite effects would be expected if a metabolite rather than the intact benzene were the toxic agent and the metabolite were not destroyed before reaching the target organ. However, the investigators found that both inhibitors (piperonyl butoxide, cobaltous chloride) and an inducer (phenobarbital) of microsomal cytochrome P-450 tended to reduce the toxicity of subcutaneously administered benzene, suggesting a complex relationship between its metabolism and toxicity. Only pretreatment with benzene potentiated the toxicity. The most significant effect of such benzene pretreatment was a six-fold increase in quinol excretion, indicating a possible role of this metabolite or a precursor in benzene toxicity. The mechanism of benzene action remains unsettled and continues to be a source of active investigation.

To retain perspective on the possible hazard of benzene, it is important to bear in mind the relative exposures from various sources. An industrial worker exposed to the contested standard of 1 ppm would inhale approximately 10 mg benzene during an 8-hour day, or about 1000 times the amount in 1 pound of irradiated beef. Benzene has been reported in many natural foods including meat, fish, vegetables, nuts, dairy products, eggs, and beverages (Van Straten, 1977). There is evidence that conventional cooking will produce an increase in benzene, and "large" amounts have been reported in boiled beef and beef stew (Chang and Peterson, 1977).

Toluene

The well-established toxicity of benzene to blood and blood-forming organs has also been attributed to toluene, partly because of structural similarities and partly because impure preparations of toluene produce benzene-like toxicity (NIOSH, 1973). Contamination with benzene has rendered many toluene toxicity studies inconclusive because commercially available toluene may contain as much as 25 percent benzene (EPA, 1978). Studies using purified toluene have failed to demonstrate a myelotoxic effect (NIOSH, 1973, EPA, 1978). In fact, a recent study suggests that toluene may actually exert a protective effect against the hematopoietic toxicity of benzene (Andrews et al., 1977). Toluene (1720 mg/kg) and benzene (440 and 880 mg/kg) were injected subcutaneously in adult, male, Swiss albino mice. This treatment reduced markedly the level of benzene metabolites in urine and bone marrow and reduced also the benzene-induced inhibition of ^{59}Fe uptake by erythrocytes. However, the concentration of benzene in bone marrow was not reduced, thus providing support for those contending that a benzene metabolite(s) is the myelotoxic agent. Toluene has also been shown to inhibit the biotransformation of styrene (Ikeda et al., 1972) and trichloroethylene (Ikeda, 1974).

Reports prior to 1973 on the health aspects of toluene were reviewed by NIOSH (1973) and subsequent literature by Hayden et al. (1977) and an EPA committee (1978). The main toxic effect of toluene appears to be upon the central nervous system. Weiss et al. (1978) reported an excitatory effect of toluene in key-pecking behavior of pigeons at an atmospheric concentration of 800 ppm, but a depressant effect at 3200 ppm. Takeuchi and Hisanaga (1977) attempted to detect central nervous effects by studying the electroencephalographic changes during spontaneous sleep of rats exposed to various atmospheric levels of toluene for 4 hours. The investigators concluded that 1000 ppm of toluene vapor prevented sleep from entering the slow-wave phase but facilitated its entry into the paradoxical phase. Concentrations of 2000 and 4000 ppm produced sleep disturbances, including myoclonic seizures at both levels.

In healthy, adult men, reaction time was impaired by 20-minute exposure to 300 ppm toluene in inspired air. Exposure to 700 ppm toluene was necessary to produce significant impairment in perceptual speed, measured by the time required to identify identical numbers in 60 separate columns (Gamberale and Hultengren, 1972). Lewis and Patterson (1974) observed various symptoms, including mental confusion, exhilaration, and fatigue when human subjects were exposed for 3 hours at 600 ppm.

Reports are rare of toxic effects by toluene on other organ systems. Bruckner and Peterson (1976) failed to detect any injury to lung, liver, or kidney in mice exposed to 4000 ppm of toluene vapor for 3 hours daily, 5 days per week, for up to 8 weeks. Cardiac arrythmias (Reinhardt et al., 1971) and renal tubular acidosis (Taher et al., 1974) have been associated with toluene "sniffing" but the specific role of toluene was not established definitively. Hayden et al. (1977) in a recent review concluded that there is little firm evidence that toluene exerts a specific toxic effect on any organ system.

The Chemical Industry Institute of Toxicology has instituted an investigation of the possible toxic and carcinogenic effects of toluene following chronic inhalation exposure to a commercial product (containing 100 ppm benzene). Only preliminary results are available (EPA, 1977). Groups of 30 rats each (strain and age not stated) were exposed to 30, 100, 300, or 1000 ppm of the commercial toluene preparation for 90 days. No significant differences from controls were noted in body weight, hematology, blood and urine chemistries, or frequency of histopathologic changes. Alopecia around the ears occurred in some female rats and red deposits or discharges from the nose and eyes were noted in some male rats. The nature of the red discharge was not indicated.

The concentrations of toluene in irradiated beef were 50 to 65 µg per kg, approximately the same as in thermally sterilized beef. Toluene has been detected in about 30 foods, with concentrations of 500 µg per kg in refrigerated fish. Average air samples in different cities ranged from 11 to 140 µg per m^3 (LSRO, 1977). Concentrations in single and composite samples of industrial water effluents have been found to range from 40 to 280 µg per l (EPA, 1978).

Xylene

Xylene is found only in trace amounts in beef (4 µg/kg) and is not a radiolytic product.

B. OXYGEN CONTAINING COMPOUNDS

1. Alcohols (pp. 68-72)

The only alcohols detected in irradiated beef were methanol and ethanol. Publications concerning the toxicology of these compounds, especially the latter, continue to appear, adding to an already mammoth bibliography. However, none of the recent publications is relevant to the present discussion or modifies the original report (LSRO, 1977).

2. Aldehydes (pp. 73-79)

The following aldehydes were detected in irradiated beef in concentrations from 10 to 398 µg per kg: 2-methyl pentanal, undecanal, dodecanal, tetradecanal, pentadecanal, hexadecanal, octadecanal, hexadecenal, and octadecenal. No recent study on any of these aldehydes has come to the attention of the Select Committee.

3. Ketones (pp. 80-87)

Only the two simplest ketones, acetone and methyl ethyl ketone (MEK, 2-butanone) were detected in irradiated beef. Both are widely used as industrial solvents and both have low acute toxicities. Browning (1965) cited studies in which workers have been exposed to 1000 to 2000 ppm of acetone for years with no ill-effects other than temporary headaches or anorexia. Similarly, the effects of MEK exposure are generally reported to be mild and temporary (Elkins, 1959). However, Viader et al. (1975) reported a case of neuropathy in a worker exposed for 2 years to a tetrahydrofuran-based glue containing MEK as the solvent.

Couri and coworkers (1977) have studied the influence of inhaled vapors of several ketones on young Wistar rats. Rats were exposed to 750 ppm of MEK, 225 ppm of methyl n-butyl ketone (MBK, 2-hexanone), or a mixture of MEK/MBK. Hexobarbital sleeptimes were significantly reduced following exposure to MEK or to the mixture of MEK with MBK, but not to MBK alone. Hepatic microsomal activities of various enzymes (aniline hydroxylase, aminopyrine demethylase, neoprontosil reductase, p-nitrobenzoate reductase) increased two- to three-fold in the MEK and MEK/MBK exposure groups compared with controls.

Exposure to MBK causes peripheral neuropathy similar to that already described for hexane (p. 2). Both hexane and MBK have a common metabolite, 2, 5-hexanedione, and this is believed to be the toxic principle (Couri et al., 1978). Cats, rats, and chickens chronically exposed to MBK vapors developed neuropathic signs, while those exposed to MEK did not (Prockop and Couri, 1977). However, a more rapid and severe toxicity was observed with combined vapors of MEK/MBK than with MBK alone. Two of six rats exposed to vapors of MBK (400 ppm) exhibited mild neuropathy, but no fatalities, during 60 days of continuous exposure. In the MEK/MBK (750/225 ppm) group, the experiment was limited to 23 days because of the severity of the neuropathy, with all six rats dying during exposure, or within 2 weeks after removal from the exposure chamber (Abdel-Rahman et al., 1976).

The recent report of Altenkirch et al. (1977) suggests that MEK in high concentrations may have neurotoxic effects. These investigators described a sudden outbreak of polyneuropathy among 18 young people sniffing a glue thinner containing hexane and MEK. These individuals had sniffed the same brand of thinner, containing 31 percent hexane, 30 percent toluene, 28 percent ethyl acetate, and 11 percent of other hydrocarbons, for up to 7 years, without apparent ill-effects. There had been no reported adverse effects among an estimated 2000 adolescents who had sniffed this product for various periods of time. In the early summer of 1975, the formulation of the thinner was changed to contain 11 percent MEK and 16 percent hexane. The other constituents remained approximately the same. The new thinner caused neurological symptoms in the 18 victims almost identical with those reported elsewhere with hexane. No further cases have been observed since the original formulation was restored in January, 1976.

C. SULFUR-CONTAINING COMPOUNDS (pp. 88-94)

Four sulfides (carbonyl sulfide, dimethyl sulfide, dimethyl disulfide, and hydrogen sulfide) and one thiol (ethane thiol) were detected in irradiated beef at concentrations of 2 to 10 µg per kg (2 to 10 parts per billion). Each of these compounds has been found in commonly consumed foods at levels two to five orders of magnitude greater than these amounts (LSRO, 1977) and

only ethyl mercaptan and dimethyl sulfide showed any increased concentrations after irradiation (10 g/kg). No recent publications on the biological effects of these substances could be found.

D. NITROGEN-CONTAINING COMPOUNDS (pp. 95-98)

Acetonitrile was the only volatile nitrogen-containing compound detected in irradiated beef. The concentration was extremely low (1 to 3 g per kg) and less than that found in frozen controls or thermally sterilized beef, indicating a nonradiolytic origin.

E. HALOGEN-CONTAINING COMPOUNDS (pp. 99-105)

Tetrachloroethylene (perchloroethylene) was the only halogen-containing compound detected in irradiated beef. It was found in some, but not all samples of irradiated beef, and in some nonirradiated samples as well. The compound was shown to be of extraneous rather than of radiolytic origin.

III. DISCUSSION (pp. 107-108)

Recent reports emphasize the potential risk to industrial workers and solvent abusers chronically exposed to appreciable levels of several readily available volatile compounds. The reported toxicity in virtually all these experimental and clinical studies has resulted from inhalation of 10 to 1000 ppm or more of these compounds for extended periods of time. The quantities inhaled from these exposures are several orders of magnitude greater than would be ingested from the consumption of even large amounts of irradiated beef. Each of the radiolytic compounds discussed in this report are found naturally in various commonly consumed foods.

IV. CONCLUSION (p. 109)

The Committee reaffirms its original conclusion that there is no evidence to suggest that the volatile radiolytic compounds found in beef irradiated in the described manner would constitute a hazard to health of the consumer.

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